REMARKS

Claims 1-158 have been canceled and claims 159-259 have been added. The Examiner has acknowledged that claims 47 and 49 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims; these claims have been rewritten as claims 250 and 252. The Examiner has also acknowledged that claim 48 is free of prior art but is rejected for other reasons; this claim has been rewritten as claim 251.

Support for claims 159-259 may be found in Appendix A, which correlates the newly added claims to the cancelled claims and also provides citations to the specification.

The terms "Xpress" and "FLAG" have been canceled from the claims, and the sequence of the FLAG epitope has been inserted; support for this sequence may be found at page 39, lines 18-22 and page 41, lines 22-24.

A. REJECTION OF CLAIMS 48 AND 61-73 UNDER 35 U.S.C. § 112, ¶ 2

Reconsideration is requested of the rejection of claims 48 and 61-73 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

On page two of the Jan. 16, 2004 Office Action, the Office asserts that, in claim 48, the alternative language "or" is more appropriate than the inclusive language "and." Claim 207, which replaces claim 48, has been drafted in accord with the Office's suggestion.

Also on page two of the Jan. 16, 2004 Office Action, the Office asserts that claims 61-73 are confusing because "$dNTP_1$" lacks proper antecedent basis in claim 46. Claim 161, which replaces claim 61, has been drafted to provide antecedent basis for $dNTP_1$.

B. REJECTION OF CLAIMS 46, 50-88, AND 136-154 UNDER 35 U.S.C. §103 OVER RAMSAY SHAW ET AL.

Reconsideration is requested of the rejection under 35 U.S.C. § 103(a) of claims 46, 50-88, and 136-154 as being unpatentable over Ramsay Shaw et al. (US 5,683,869). Newly added claims 159 and 229 replace claims 46 and 136, respectively.

A prima facie case of nonobviousness is only established when the Examiner provides (i) one or more references (ii) available to the inventor (iii) that teach (iv) a suggestion to combine or modify the references, (v) the combination or modification of which would appear to be sufficient to have made the claimed invention obvious to one of ordinary skill in the art.[1] Thus, the Examiner must explain why the prior art would "appear to show the *claimed subject matter*," and not simply the general aspects of the invention.[2] If the examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled a grant of the patent.[3]

1. The Office's nonobviousness analysis is not based upon claim as a whole because instructions have patentable weight

On page three, the Office asserts, without citation to authority, that the kit's written instructions should not be given patentable weight. But it is well established that a claim must be viewed as a whole in determining obviousness.[4] As the Court of Claims and Patent Appeals has stated, the "fact that printed matter by itself is not patentable subject matter ... is no reason for ignoring it when the claim is directed to a combination."[5] More recently, the Federal Circuit directly instructed that the "PTO may not disregard claim limitations comprised of printed matter."[6] Thus, the Office should consider "all of the limitations of the claims, including printed matter limitations, in determining whether the invention would have been obvious."[7]

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[1] *See In re Lintner*, 458 F.2d 1013, 173 USPQ 560, 562 (C.C.P.A. 1972); *In re Fielder*, 471 F.2d 640, 176 USPQ 300, 302 (C.C.P.A. 1973).
[2] *In re Rhinehart*, 531 F.2d 1048, 189 USPQ 143, 147 (C.C.P.A. 1976).
[3] *In re Oetiker*, 977 F.2d 1443, 24 USPQ 2d 1443 (Fed. Cir. 1992).
[4] *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966).
[5] *In re Miller*, 164 USPQ 46, 49 (CCPA 1969).
[6] *In re Lowry*, 32 F.3d 1579, 1582 (Fed. Cir. 1994).
[7] *In re Gulack*, 703 F.2d 1381, 217 USPQ 401 (Fed. Cir. 1983).

The kit of claim 159 is a combination of non-printed matter (deoxynucleotidetriphosphate mixture) and printed matter (instructions). The inclusion of "instructions for using the deoxynucleotidetriphosphate mixture in a procedure for directionally ligating a nucleic acid into a first adaptor sequence" is an express requirement present within the claim. As such, the Office "cannot dissect [the] claim, excise the printed matter from it, and declare the remaining portion of the mutilated claim to be unpatentable. The claim must be read as a whole."[8]

The instructions in claim 159 are related functionally to the balance of non-printed matter elements in the kit. The Federal Circuit has held that printed matter, if functionally related to other claim elements, is to be given patentable weight.[9] The test to apply is whether there exists any new and unobvious functional relationship between the printed matter and other claim elements.[10] The instructions dictate a procedure that enables use of the deoxynucleotidetriphosphate mixture containing modified deoxynucleotidetriphosphates to directionally ligate a double-stranded nucleic acid to an adaptor sequence. The specification is replete with enabling details for this procedure. The instructions facilitate directional ligation with the kit of the present application. In sum, the instructions perform a function.

Where the Office seeks to ignore a printed matter limitation, **the Office has the burden of establishing the absence of a novel, nonobvious functional relationship between the printed matter and other claim elements in order to establish a prima facie case of obviousness.**[11] Because the Office ignored the instructions limitation of claim 155, the Office failed to establish that the printed instructions, within the context of the entire claims, lack a new and nonobvious functional relationship with the deoxynucleotidetriphosphate mixture containing modified deoxynucleotidetriphosphates. This argument applies equally to claims dependent upon claim 159, such as claims 160-228.

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[8] *In re Gulack*, 703 F.2d at 1385.
[9] *Id.*
[10] *Id.* at 1386; *In re Lowry*, 32 F.3d at 1382..
[11] *In re Lowry*, 32 F.3d at 1384.

2. Ramsay Shaw et al. do not disclose a directional ligation kit

Ramsay Shaw et al. disclose a "one-step solution to cycle sequencing" through omission of purification steps.[12] Furthermore, Ramsay Shaw et al. only disclose use of exonuclease resistant deoxynucleotidetriphosphates as markers for detecting location during sequencing.[13] Ramsay Shaw et al. do not expressly disclose or suggest the use of modified deoxynucleotidetriphosphates for ligation or kits useful for ligation, nor is such use inherent.

Furthermore, merely because deoxynucleotidetriphosphate-containing sequences are resistant to exonuclease digestion does not make the use of deoxynucleotidetriphosphates in ligation obvious. The Federal Circuit has held that the "inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."[14] Further, general skill in the art will rarely operate to supply missing knowledge or prior art to reach an obviousness judgment, for this approach is too vulnerable "to the insidious effect of a hindsight syndrome."[15]

The Office has failed to show how Ramsay Shaw et al. disclose or suggest the use of modified deoxynucleotidetriphosphates and instructions for ligation of double-stranded nucleic acid into an adaptor sequence so as to make such a kit obvious to one skilled in the art. Because the Office fails to satisfy this element, the Office has failed to meet its burden of establishing a prima facie case of obviousness. This argument applies equally to claim 159 and all claims dependent upon claim 159.

3. Ramsay Shaw et al. do not disclose a *mixture* with dATP, dGTP, dCTP, dTTP and at least two modified dNTPs

Applicant respectfully points out that claims 229-249, as rewritten from cancelled claims 136-154, are drawn to deoxynucleotidetriphosphate mixtures rather than kits containing mixtures as asserted by the Office on page three.

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[12] Ramsay Shaw et al., US Patent No. 5,683,869, col. 9, ln. 48.
[13] *Id.* at col. 8, ln. 39-45
[14] *In re Spormann*, 363 f.2d 444, 150 USPQ 449, 452 (CCPA 1966).

The Office asserts that Ramsay Shaw et al. use deoxynucleotidetriphosphate mixtures comprising two or three modified nucleotides. The mixtures that contain two or three modified nucleotides, however, substitute boronated triphosphates for the unmodified equivalent. For example, Ramsay Shaw et al. disclose PCR reaction with "normal triphosphates except that boronated triphosphates were substituted for the normal one(s) as follows ... boronated dGTP+dATP ...."[16] Thus, a Ramsay Shaw et al. mixture that contains modified dGTP and modified dATP contains no unmodified dATP or unmodified dGTP. In contrast, claim 229 requires a deoxynucleotidetriphosphate mixture that contains dATP, dGTP, dCTP, dTTP, and two or more modified deoxynucleotidetriphosphates. Ramsay Shaw et al., therefore, do not disclose the mixture of claim 229 and the claims depending therefrom.

Claims 230-249 also require certain ratios of modified to unmodified deoxynucleotidetriphosphates of the same type. Because Ramsay Shaw et al. do not include modified and unmodified deoxynucleotidetriphosphates of the same type in their mixtures, the ratios of claims 230-249 could not be disclosed, expressly or inherently, by Ramsay Shaw et al.

Claims 238-243 recite alpha thiophosphorano deoxynucleotidetriphosphates. In contrast, Ramsay Shaw et al. only disclose mixtures containing boronated deoxynucleotidetriphosphates. While they do mention alpha thiotriphosphates in the background, it is in the context of failures in the art to achieve satisfactory amplification.

4. No suggestion to modify Ramsay Shaw et al.

Ramsay Shaw et al. fail to suggest modifying the disclosed methodology so as to generate a kit containing modified deoxynucleotidetriphosphates and instructions for use of the kit for directionally ligating a double stranded nucleic acid to an adaptor sequence. A prima facie case of obviousness requires some reason, suggestion, or motivation from the prior art for the person of ordinary skill to have modified the references. The use of modified deoxynucleotidetriphosphates is merely a general

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[15] *W.L. Gore & Assocs. V. Gorlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-313 (Fed. Cir. 1983), *cert. denied*, 469 US 851 (1984).

aspect of both the Ramsay Shaw et al. and Applicant's claim 159. But Ramsay Shaw et al. do not "appear to show the claimed subject matter"[17] of applicant's claim 159, *i.e.*, the kit with modified deoxynucleotidetriphosphates and instructions for the use of the kit for directionally ligating a double stranded nucleic acid to an adaptor sequence.

Ramsay Shaw et al. also fail to suggest that such a directional ligation kit would be useful in the one-step sequencing techniques that are the focus of their patent. Throughout, Ramsay Shaw et al.'s use of modified deoxynucleotidetriphosphates is limited to one-step sequencing through the omission of purification steps. In fact, in describing prophetic potential uses of their invention, Ramsay Shaw et al. list only processes which involve one-step sequencing; for example, time savings in shotgun method sequencing by omission of purification steps, direct sequencing of Alu PCR products, increasing the rate of population diversity sequence data collection in the human genome project, and time acceleration of disease diagnosis by genotype sequencing.[18]

Because Ramsay Shaw et al. provide no reason, suggestion, or motivation to modify the disclosed one-step sequencing procedures to encompass a direction ligation kit as featured in claim 159 of the present application, the Office has failed to establish a prima facie case of obviousness. This argument applies equally to those claims dependent upon claim 159.

Furthermore, the Office has failed to come forward with any reason, suggestion, or motivation to modify the ratios and concentrations of deoxynucleotidetriphosphates disclosed in Ramsay Shaw et al. in order to meet the specific challenges posed by direct ligation applications and addressed by features of claims 161-167, 169-172, 174-176, 179-181, 183-188, 190-192, 196-199, 230-232, 234-237, 240-243, and 246-249.

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[16] Ramsay Shaw et al., US Patent No. 5,683,869, col. 6, ln. 57-67; Figure 8; Example 7.
[17] *In re Rhinehart*, 189 USPQ at 147.
[18] Ramsay Shaw et al., US Patent No. 5,683,869, col. 11-12.

5. Additional features contribute to nonobviousness

Furthermore, several dependent claims add additional features that are nonobvious to one skilled in the art. On page 4, the Office asserts that the various ratios of modified versus unmodified deoxynucleotidetriphosphates (presumably claims 161-167, 169-172, 174-176, 179-181, 183-188, 190-192, 196-199, 230-232, 234-237, 240-243, and 246-249, though the Office does not cite any specific claims)[19] are merely routine optimizations not contributing to non-obviousness, but the Office provides no basis for such conclusion. The Office has the initial burden of coming forward with substantiated reasons supporting an obviousness rejection, which here it has not done.

An example of a feature provided by ratios of modified versus unmodified deoxynucleotidetriphosphates is provided in the following passage: an "acceptable ratio is obtained when a compromise between amplification toxicity is minimized and protection against exonuclease digestion is maximized."[20] The Office has failed to point out that such a compromise was appreciated or known to be necessary in the art.

As another example, differing ratios of modified versus unmodified deoxynucleotidetriphosphates allows tailoring of amplicon termination at statistically determined positions. *See* Example 3, p. 49, ln. 12-18; p. 50, ln. 5-13; p. 52, ln. 8-11. The Office has failed to point out that such a relationship between the ratio of modified vs. unmodified deoxynucleotidetriphosphates and termination at statistically determined positions was appreciated in the art. While the Office points to Example 2 of Ramsay Shaw et al., this example discusses optimization for the purpose of ensuring that each molecule was digested only to, and not beyond its point of insertion.

For these reasons, the Office has failed to meet its initial burden of coming forward, and as such, failed to show a prima facie case of obviousness with respect to these claims.

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[19] These new claims derive support in part from cancelled claims derive support in part from cancelled claims 61-64, 66-68, 71, 73, 75-79, 81-83, 86, 88, 141-145, 147-149, and 152-154).

[20] Application 10/002,292, p. 29, ln. 16-19.

C. REJECTION OF CLAIMS 46, 50, AND 136 UNDER 35 U.S.C. §103 OVER WALKER

Reconsideration is requested of the rejection under 35 U.S.C. § 103(a) of claims 46, 50, and 136 as being unpatentable over Walker (US 5,455,166). Claims 159, 227, and 229, at least in part, correspond to cancelled claims 46, 50, and 136. The arguments made with respect to Ramsay Shaw et al. apply equally to Walker. In brief, the Office improperly ignored the claim element of instructions; failed to show how Walker suggests a directional ligation kit, as claimed; and failed to show how Walker suggests modifying the disclosure so as to provide for such a directional ligation kit. As discussed above, for these reasons the Office has failed to show a prima facie case supporting the obviousness rejection.

The deoxynucleotidetriphosphate mixtures of Walker substitute modified deoxynucleotidetriphosphates for their unmodified equivalent. For example, Walker discloses "a mixture comprising an excess of all four deoxynucleotidetriphosphates, wherein at least one of which is substituted ...."[21] Similarly, Walker discloses a mixture of dATP, dGTP, dTTP, and alphathio-dCTP in Example 1 and dCTP, dGTP, dTTP, and alphathio-dATP in Examples 2-3 —notably these Walker mixtures do not contain dCTP and dATP, respectively.

In contrast, the kit of claim 186 (which replaces claim 75) and the mixture of claim 229 (which replaces claim 136) recite a deoxynucleotidetriphosphate mixture that contains dATP, dGTP, dCTP, dTTP, and two or more modified deoxynucleotidetriphosphates. Therefore, Walker does not disclose the mixture recited in claims 186 and 229. This argument applies equally to claims 186 and 229 and claims dependent thereof.

Also, claims 186-188, 190-192, 196-199, 230-232, 234-237, 240-243, and 246-249 recite ratios relating two pairs of modified and unmodified deoxynucleotidetriphosphates of the same type. These ratios are not disclosed in Walker because the mixtures of Walker do not contain two pairs of modified and unmodified deoxynucleotidetriphosphates of the same type.

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[21] Walker, U.S. Patent 5,455,166, col. 7, ln. 11-14.

Furthermore, Walker pertains to strand displacement amplification, where a thionucleotide is incorporated during primer extension to confer endonuclease resistance to create restriction sites that get nicked rather than cleaved by a restriction enzyme. In fact, the claims and specification of Walker require a DNA polymerase that lacks 5'-3' exonuclease activity. In contrast, claims 212-214 and 253-259 feature an exonuclease while claim 160 features instructions for using an exonuclease with the deoxynucleotidetriphosphate mixture.

CONCLUSION

In light of the foregoing, Applicants request an entry of the specification amendment, claim amendments, and abstract amendments; request a withdrawal of claim rejections; and solicit allowance of the claims. The Office is invited to contact the undersigned attorney should any issue remain unsolved.

A check in the amount of $950.00 is enclosed. The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

Edward J. Hejlek, Reg. No. 31,525
SENNIGER, POWERS, LEAVITT & ROEDEL
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

EJH/DJH/lrw

APPENDIX A

The following table provides support for newly added claims 155-255.

New Claims	Corresponding Cancelled Claims	Specification Support
159	46; 19	p. 7, ln. 11-16; p. 12, ln. 26-28; p. 13, ln. 9-22; p. 20, ln. 26 – p. 21, ln. 14; p. 21, ln. 27-30; p. 22, ln. 22-27; p. 50, ln. 9-10; p. 51, ln. 14
160		
161	61, 62	
162	63	
163	64	
164	54, 65	
165	66	
166	67	
167	68	
168	55	
169	58, 69	
170		p. 26, ln. 20-28
171		p. 26, ln. 20-28
172		p. 26, ln. 20-28
173	69	
174		p. 26, ln. 29-33
175		p. 26, ln. 29-33
176		p. 26, ln. 29-33
177	55, 70	
178	58, 60, 70	
179	71	
180		p. 27, ln. 1-9
181		p. 27, ln. 1-9
182	72	
183	73	
184		p. 27, ln. 9-14
185		p. 27, ln. 9-14
186	74, 75, 76, 77	
187	78	
188	79	
189	80	
190	81	
191	82	
192	83	
193	84, 85	

194	85	p. 27, ln. 32 - p. 28, ln. 2
195	85, 86	p. 28, ln. 7-18
196		p. 28, ln. 7-18
197		p. 28, ln. 7-18
198		p. 28, ln. 7-18
199	86	p. 28, ln. 7-18
200	87	p. 28, ln. 19-20
201		p. 28, ln. 19-22
202		p. 28, ln. 22-29
203		p. 28, ln. 22-29
204		p. 28, ln. 22-29
205	88	
206	47	
207	48	
208	49	
209		p. 33, ln. 27; p. 36, ln. 33 p. 37, ln. 9; p. 38, ln. 14-23; p. 39; p. 42, ln. 22-27
210	48	
211	49	
212	51	
213	52	
214	53	
215		p. 4, ln. 27-33; p. 14, ln. 4-20; p. 15, ln. 7-10; p. 16, ln. 21 - p. 17, ln. 17, ln. 17
216		p. 17, ln. 18-30
217		p. 17, ln. 18-30
218		p. 17, ln. 18-30
219		p. 17, ln. 18-30
220		p. 17, ln. 30 - p. 19, ln. 3
221		p. 17, ln. 30 - p. 19, ln. 3
222		p. 17, ln. 18 p. 19, ln. 3
223		p. 14, ln. 6-9; p. 15, ln. 7; p. 19, ln. 24-26; p. 20, ln. 20-23
224		p. 19, ln. 24-26
225		p. 20, ln. 2-6

226		p. 20, ln. 16-24
227	50	
228	50	
229	136	
230	141, 142, 143	
231	144	
232	145	
233	146	
234	147	
235	148	
236	149	
237		p. 28, ln. 8-11
238	151	p. 28, ln. 8-11
239		p. 28, ln. 8-11
240		p. 28, ln. 8-18
241		p. 28, ln. 8-18
242		p. 28, ln. 8-18
243	152	p. 28, ln. 8-18
244	153	p. 28, ln. 19-20
245	153	
246		p. 28, ln. 19-29
247		p. 28, ln. 19-29
248		p. 28, ln. 19-29
249	154	p. 28, ln. 19-29
250	47	p. 12, ln. 26-28
251	48	p. 39, ln. 18-22; p. 41, ln. 22-24
252	49	p. 39, ln. 18-22; p. 41, ln. 22-24
253	46, 50, 51	p. 7, ln. 11-16; p. 12, ln. 26-28; p. 13, ln. 9-22; p. 14, ln. 6-9; p. 20, ln. 2-6; p. 15, ln. 7; p. 19, ln. 24-26; p. 20, ln. 13-23; p. 20, ln. 26 – p. 21, ln. 14; p. 21, ln. 27-30; p. 22, ln. 22-27; p. 50, ln. 9-10; p. 51, ln. 14
254	49	
255	85, 86	p. 28, ln. 7-18
256		p. 17, ln. 30 - p. 19, ln. 3
257	53	
258		p. 20, ln. 2-6
259		p. 20, ln. 20-23